

# Cochrane for Clinicians

*Putting Evidence into Practice*

These are summaries of reviews from the Cochrane Library.

This series is coordinated by Corey D. Fogleman, MD, Assistant Medical Editor.

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**CME** This clinical content conforms to AAFP criteria for continuing medical education (CME). See CME Quiz Questions on page 542.

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## Selective Serotonin Reuptake Inhibitors for Fibromyalgia

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### Clinical Question

Would a selective serotonin reuptake inhibitor (SSRI) improve worsening fatigue, pain, and depression in a patient with fibromyalgia?

### Evidence-Based Answer

SSRIs may have a small to moderate effect on pain (number needed to treat [NNT] = 10), global improvement (NNT = 7), and depression (NNT = 13) in patients with fibromyalgia, but the quality of evidence is very low because of bias and small studies. SSRIs do not reduce fatigue related to fibromyalgia.<sup>1</sup> (Strength of Recommendation: B, based on very low-quality randomized controlled trials.)

### Practice Pointers

Fibromyalgia is a poorly understood disorder characterized by chronic, widespread pain that is often complicated by severe fatigue, mood disturbance, and sleep difficulties.<sup>2</sup> It affects 2% to 8% of the population, depending on the diagnostic criteria used.<sup>2,3</sup> The widespread nature of the pain and confirmation of a biologic basis of the disorder via brain neuroimaging have led clinicians to believe that SSRIs may be helpful in managing the symptoms of the disorder.

This Cochrane meta-analysis reviewed eight double-blind randomized controlled trials that included 383 patients.<sup>1</sup> The only SSRIs examined were citalopram (Celexa), fluoxetine (Prozac), and paroxetine (Paxil), and the studies lasted from four to 16 weeks. The overall quality of evidence from the studies was judged to be very low because of the small number of participants as well as concerns about bias, including pharmaceutical funding in a majority of the trials. The authors evaluated seven primary

outcomes and four secondary outcomes for this review.

Six of the eight studies examined whether patients had at least 30% pain reduction. SSRIs were superior to placebo, but the confidence interval (CI) was wide (NNT = 10; 95% CI, 5 to 100). SSRIs were also superior to placebo in global improvement measures (NNT = 7; 95% CI, 4 to 17). Two of the eight studies compared SSRIs with other active drugs, including amitriptyline and melatonin, for the outcomes of 30% pain reduction and global improvement, and did not show a statistically significant difference.

SSRIs were found to be superior to placebo for depression symptoms in patients with fibromyalgia (NNT = 13; 95% CI, 7 to 37), although they were not significantly different compared with other active agents. There were no statistically significant differences in measures of fatigue or sleep problems. SSRIs were found to be as tolerable and safe as placebo.

SSRIs were also superior to placebo for improvements in pain intensity (standardized mean difference [SMD] = -0.37; 95% CI, -0.69 to -0.04) as well as disease-specific quality of life (SMD = -0.70; 95% CI, -1.12 to -0.28). No significant differences were noted between SSRIs and other active agents for these secondary outcomes. There were also no differences between SSRIs and placebo for physical functioning, anxiety, or tenderness.

Although a small, statistically significant benefit was detected for 30% pain reduction, global improvement, and depression with SSRIs vs. placebo in this meta-analysis, the quality of evidence was very low because of the limited numbers of patients and the potential for attrition and reporting bias. Five of the eight studies were sponsored by drug companies. Limitations of the analysis include different outcome assessment tools used in various studies, low number of studies because of strict exclusion criteria, and short study lengths (i.e., none longer than four months). Despite the limited evidence, the Department of Veterans Affairs/

Department of Defense clinical practice guideline for chronic multisystem illness, which includes fibromyalgia, suggests considering SSRIs as an adjunctive treatment.<sup>4</sup> The positive results in some studies and the limited therapies available for fibromyalgia suggest that more research is warranted.

The practice recommendations in this activity are available at <http://summaries.cochrane.org/CD011735>.

EDITOR'S NOTE: The NNTs reported in this Cochrane for Clinicians were calculated by AFP medical editors from raw data provided in the original Cochrane review.

The views presented in this article are those of the authors and do not represent the views of the U.S. Army, the U.S. Air Force, the Department of Defense, or the U.S. government.

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## Topical Tacrolimus for Eczema

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### Clinical Question

Is topical tacrolimus (Protopic) safe and effective for the treatment of eczema?

### Evidence-Based Answer

For children and adults with moderate to severe eczema, topical tacrolimus is an effective, albeit costly, alternative to topical corticosteroids. Both tacrolimus strengths (0.03% and 0.1%) are superior to low-potency topical corticosteroids, whereas tacrolimus 0.1% has similar effectiveness to moderate- to high-potency topical corticosteroids. A mild, self-limited, local burning sensation is

common with use.<sup>1</sup> (Strength of Recommendation: A, based on consistent, good-quality patient-oriented evidence.)

### Practice Pointers

Although topical corticosteroids are the mainstay of treatment for eczema, they can cause skin atrophy on sensitive areas such as the face, eyelids, genitalia, and intertriginous zones. Topical calcineurin inhibitors such as tacrolimus, pimecrolimus (Elidel), and cyclosporine (Sandimmune) are immunosuppressants that do not cause skin atrophy.

The authors of this Cochrane review evaluated 20 randomized controlled trials with 5,885 participants from North America, Europe, Asia, and Africa.<sup>1</sup> The trials compared topical corticosteroids with topical calcineurin inhibitors (primarily tacrolimus) in the treatment of moderate to severe eczema and included adults and children six months or older. Treatment duration ranged from two weeks to one year. Most of the studies were considered high quality with a low risk of bias. Both low- and high-potency tacrolimus (0.03% and 0.1%) were included. Primary outcomes were physician and participant assessments of global improvement (more than 90% subjective improvement being “clear or excellent”) and adverse effects.

The various trial regimens and durations limited the ability of the reviewers to carry out meta-analyses. In studies of children, low-potency tacrolimus (0.03%) was consistently better at achieving physician-assessed improvement than low-potency twice-daily topical corticosteroids. One study reported on the use of once-daily tacrolimus dosing (n = 411; relative risk [RR] = 2.05; 95% confidence interval [CI], 1.36 to 3.08), whereas two studies reported on the use of twice-daily tacrolimus dosing (n = 790; RR = 2.58; 95% CI, 1.96 to 3.38).

In two studies of 1,349 adults, those receiving tacrolimus 0.1% had similar outcomes at three and 12 months to patients receiving mid-potency topical corticosteroids. In one of the studies (n = 972), patients and physicians reported more improvement at six months with tacrolimus 0.1% than did patients and physicians in the topical corticosteroids group (RR = 1.21; 95% CI, 1.13 to

1.29 for patient report; RR = 1.32; 95% CI, 1.17 to 1.49 for physician report). In three studies of 543 patients, tacrolimus 0.1% was better than pimecrolimus 1% in achieving physician-assessed global improvement (RR = 1.80; 95% CI, 1.35 to 2.42). Tacrolimus 0.03% was also somewhat better than pimecrolimus 1% in one study of 139 children (RR = 1.42; 95% CI, 1.02 to 1.98). When comparing the two tacrolimus potencies in six studies of 1,640 patients, the 0.1% potency led to modestly superior physician-assessed improvement scores (RR = 0.82; 95% CI, 0.72 to 0.92).

Regarding tacrolimus use in children, there was no significant difference in the outcome of physician-assessed improvement when patients received once-daily vs. twice-daily dosing, nor between patients treated with high- vs. low-potency strengths.

A local burning sensation was reported by 20% to 60% of participants treated with tacrolimus, but this was generally mild and self-limited. No other adverse effects were more common with tacrolimus.

The U.S. Food and Drug Administration has issued a boxed warning based on animal studies and case reports suggesting a possible association between topical calcineurin inhibitors and lymphoma and skin

malignancies.<sup>2</sup> An excess of malignancies was not observed in the trials reviewed in this Cochrane analysis, although they were not of sufficient size to detect this outcome. Guidelines from the U.S. Food and Drug Administration and the American Academy of Dermatology state that topical calcineurin inhibitors should be second-line therapy for eczema because of their high cost and the potential for minor and more serious adverse effects.<sup>2,3</sup> However, the American Academy of Dermatology guidelines do allow for off-label use of low-dose topical calcineurin inhibitors in children younger than two years.<sup>3</sup>

The practice recommendations in this activity are available at <http://summaries.cochrane.org/CD009864>.

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